genes identified by microarray analysis. The reported data demonstrate that the lengths of the acyl chains are increased in the *fapR* mutant strain (which probably accounts for the cold-sensitive growth), but the total numbers of acyl chains were not reported. Increased acyl chain length means that more carbon is being converted to fatty acids and thus constitutes a form of overproduction, although the increase in carbon incorporation is very modest (15%–20%). However, it may not be possible to dramatically increase the total number of acyl chains synthesized, since there may be no sink for extra lipids, and feedback inhibition of the elongation cycle enzymes by accumulated acyl-ACPs could occur. In this regard it could be useful to express a cytosolic thioesterase to cleave the acyl chains from ACP and thereby preclude feedback inhibition and provide a sink for overproduction (Cho and Cronan, 1995).

A puzzling aspect of FapR regulation to be addressed in the future is that *fapR* is the first gene in a FapR-regulated operon of fatty acid synthetic genes, and, thus, its expression is autoregulated. Autoregulation of a transcription factor-encoding gene is a common homeostasis mechanism in bacteria, but, in general, the regulatory gene is independently transcribed, such that it can have an expression profile different from that of the genes it regulates. In the present case the physiological conditions that give increased transcription of lipid synthetic genes also would result in increased levels of FapR. This could be a device to facilitate return to basal levels of transcription. However, it also seems possible that FapR is irreversibly inactivated upon operator release and must be replaced.

FapR is clearly a central and important transcriptional regulator of lipid synthesis in a subset of gram-positive bacteria that includes several important pathogens. Although FapR homologs are not restricted to spore-forming bacteria, the regulatory system seems likely to play a role in sporulation, an event that requires increased membrane lipid synthesis.

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Welcome to Syndetome: A New Somitic Compartment

Virtually nothing was known about the embryonic origin of tendons, until a recent paper by Brent and colleagues in which they track the origin of tendon progenitors of the body axis and reveal the molecular events and tissue interactions leading to their commitment.

Posture and mobility of the vertebrate body rely on the musculoskeletal system. Full functionality of this system requires that muscles are tightly attached to the bones so that the force generated by muscles can be used to produce body movement. This link is provided by the tendons. While the embryonic origin of the muscles and the bones has been thoroughly studied, little is known about tendons development. In the limbs, tendons have been shown to derive from the lateral plate, while the tendons associated to the segmented muscles of the vertebral column derive from the somites. A recent paper by Brent and colleagues provides insights into the origins of tendon progenitors and tracks the molecular events and tissue interactions leading to their commitment (Brent et al., 2003).

Musculoskeletal elements of the body axis—vertebrae, ribs and their associated muscles—derive from the paraxial mesoderm. During its differentiation, the paraxial mesoderm undergoes segmentation and becomes organized as paired blocks of cells, the somites, distributed on both part of the neural tube along the anteroposterior (AP) axis. The somites differentiate in a very stereotypical way. Once produced, they appear as epithelial spheres with no distinct morphological polarity or signs of differentiation. A few hours later, under the influence of extrinsic signals, the ventromedial portion of the somite deepithelializes to form a distinct mass of mesenchymal cells, the sclerotome. The dorsolateral part of the somite remains epithelial and forms the so-called dermomyotome. Later on, cells derived from the dermomyotome intercalate between the sclerotome and the dorsal epithelial sheet now called dermatome to form the myotome. The sclerotome will form the bones of vertebral column, the vertebrae and ribs, while the myotome contains the precursors of the segmented body muscles that associate with these bones. The dermatome generates the dorsal dermis at the body level. At this stage, these three tissues, dermatome, myotome, and sclerotome, clearly define distinct embryological compartments: they have distinct morphologies, unique

cell fates, and specific molecular markers, and they do not intermingle. What about the tendon progenitors? Do they come from the somites? Are they mixed with any of the other compartments? How are they specified?

To address these issues, Brent and coworkers first took advantage of the expression pattern of *scleraxis*, a bHLH transcription factor identified in a two-hybrid screen for cDNAs encoding novel cell-type-specific bHLH proteins that dimerize with the ubiquitous bHLH E12 (Cserjesi et al., 1995). This gene labels all the tendons of the body axis and of the limbs (Schweitzer et al., 2001). Looking back on early development, when somitogenesis proceeds, they observed that the expression of *scleraxis* was restricted to a subset of somitic cells, lying at the anterior and posterior edge of each somite, just at the interface between the myotome and the sclerotome. Cell lineage analyses further show that this cell population derives from a dorsolateral domain of the sclerotome and will later give rise to the differentiated tendons. Moreover, closer molecular analysis indicates that there is no overlap between myotomal and sclerotomal markers (*MyoD* and *Pax1*, respectively) and *scleraxis*. In other words, this *scleraxis*-expressing cell population has a unique fate, as tendons, is segregated from the other somitic compartments, does not mix with the surrounding cells, and can be identified by specific markers. Therefore, these data clearly unravel a new somitic compartment for tendon progenitors, which the authors named the syndetome, from the Greek "syndesis," to bind together.

The next step was to understand how this population emerges during somite compartmentalization. Temporally, the syndetome is the last somitic compartment to arise. Dermomyotome ablation demonstrates that the syndetome requires a signal from this structure for its differentiation. Because it is activated in the adjacent postmitotic fibers of the myotome when *scleraxis* is observed in the syndetome, FGF8 was an attractive candidate to play a role in the induction of the syndetome. Indeed, overexpressing FGF8 in the somite strongly activates ectopic *scleraxis* expression. Unexpectedly, the response to FGF8 is not direct but involves a complex relay system in the developing myotome. FGF8 signal is relayed by *FREK*, one of the FGF receptors, which is expressed at the anterior and posterior edge of the myotome, i.e., in immature myoblasts cells directly abutting the tendon progenitors. Upon FGF8-mediated activation, *FREK* cells produce a still unknown signal that induces *scleraxis* expression in neighboring sclerotomal cells, which will ultimately become tendon progenitors. Evidence for this relay system was provided by overexpression of a dominant-negative version of FREK, which is not expressed in the syndetome and which can block *scleraxis* activation. Interestingly, upregulation of *scleraxis* in response to FGF8 is restricted to the sclerotome and occurs at the expense of *Pax1*. Consistently, overexpressing *Pax1* in the somite, either directly or indirectly as a result of *Shh* overexpression, completely abolishes *scleraxis* expression, suggesting that *Pax-1* negatively regulates *scleraxis* expression. These results show that myotome-derived FGF signaling is necessary and sufficient to induce *scleraxis* and to downregulate *Pax1* in the sclerotomal cells, which are the only somitic cells competent to form the syndetome.

This work also uncovers interesting similarities and differences between axial and appendicular tendon formation. In the limbs, *fgf4* is expressed at the extremities of muscle fibers in contact to the tendon primordia and positively regulates *scleraxis* (Edom-Vovard et al., 2002). *fgf8*, in contrast, is expressed by the tendons themselves in the limbs (Edom-Vovard et al., 2001). Also, in the limbs, tendon progenitors emerge from the lateral plate-derived mesenchyme of the limb bud, like the cartilage progenitors, whereas muscles arise from emigrating somitic cells (Chevallier et al., 1977). Therefore, both in the limbs and in the somites, tendons and cartilages share a common origin: the lateral plate-derived mesenchyme for the appendicular ones and the sclerotome for the axial ones. Furthermore, it has been established that, in the limb, initiation of tendon development is a rather autonomous process, whereas final differentiation and morphogenesis require signals from the contiguous muscles (Kardon, 1998).

These results highlight how, by close interaction between the myotome and the sclerotome, which involves both induction and repression events, tendon progenitors are precisely specified at the interface between the tissues they will link. This tight spatiotemporal regulation ensures that bones, tendons, and muscles will develop in close relationship to ultimately give rise to a functional musculoskeletal system.

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